Poster
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Taldefgrobep Alfa Improves Body Composition as Monotherapy and in Combination With Semaglutide in a DIO Mouse Model

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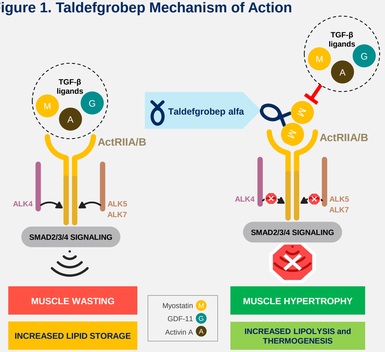
INTRODUCTION

- Obesity is a disease of excess or abnormal adipose tissue, the key driver of its pathogenic process[1-3]
- Incretin-based obesity treatments (glucagon-like peptide-1 [GLP-1] analogs) demonstrate significant weight reduction and metabolic benefits[4,5]
- Currently approved anti-obesity medications, including GLP-1 receptor agonists, achieve reductions in total body weight based on a composite loss of fat mass and loss of lean muscle mass; however, the loss of lean muscle mass with these therapeutic agents may have long-term adverse health consequences[4-7]
- Inhibition of myostatin and activin A signaling induces significant fat loss and increase in lean mass,[8,9] an ideal combination with GLP-1 receptor agonist therapy
- Taldefgrobep alfa is a novel myostatin inhibitor that selectively blocks signaling through activin II receptors and has demonstrated improvements in lean mass and loss of fat[10] (**Figure 1**)
- Taldefgrobep binds myostatin, and the taldefgrobep/myostatin complex blocks activin A and myostatin signaling
- Results from validated diet-induced obesity (DIO) mouse models have generally paralleled outcomes observed in human studies conducted in adults with obesity[11,12]

Figure 1. Taldefgrobep Mechanism of Action



ActRIIA/B, myostatin/activin type IIA/B receptor; ALK4/5/7, activin-like kinase 4/5/7; GDF-11, growth differentiation factor 11; SMAD2/3/4, mothers against decapentaplegic homolog 2/3/4; TGF-β, transforming growth factor-beta.

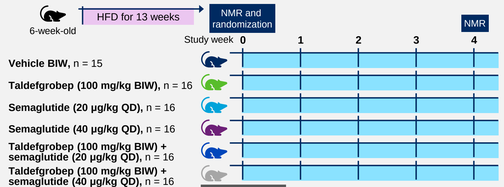
OBJECTIVE

- This high-fat diet (HFD)-induced obese mouse study was designed to evaluate the ability of taldefgrobep to impact body composition as monotherapy and in combination with semaglutide, a GLP-1 receptor agonist

METHODS

- Six-week-old C57BL/6J male mice received an HFD for 13 weeks prior to their subcutaneous treatment assignment: vehicle twice weekly (BIW), taldefgrobep 100 mg/kg BIW, semaglutide 20 µg/kg once daily (QD), semaglutide 40 µg/kg QD, taldefgrobep 100 mg/kg BIW with semaglutide 20 µg/kg QD or 40 µg/kg QD (**Figure 2**)
- Body composition (EchoMRI™) and metabolic markers were assessed at baseline, posttreatment, and study end
- Histopathology of adipose tissue, muscle, and the liver was performed
- Results from 4 weeks of dosing are presented

Figure 2. Study Schematic



BIW, twice weekly; HFD, high-fat diet; NMR, nuclear magnetic resonance; QD, once daily.

RESULTS

- Taldefgrobep monotherapy resulted in significant improvements in total body fat mass and total body lean mass at Week 4 (-26% and +15%, respectively) (**Table 1**, **Figures 3** and **4**)
- The addition of taldefgrobep to semaglutide resulted in greater reductions in fat mass and increases in lean mass relative to semaglutide alone
- Semaglutide 20 µg/kg and 40 µg/kg alone resulted in a net-negative change in lean mass at Week 4 (-3.4% and -6.5%, respectively, relative to vehicle)
  - The addition of taldefgrobep to semaglutide 20 µg/kg and 40 µg/kg resulted in significant increases in lean mass at Week 4 (+15% and +13%, respectively)

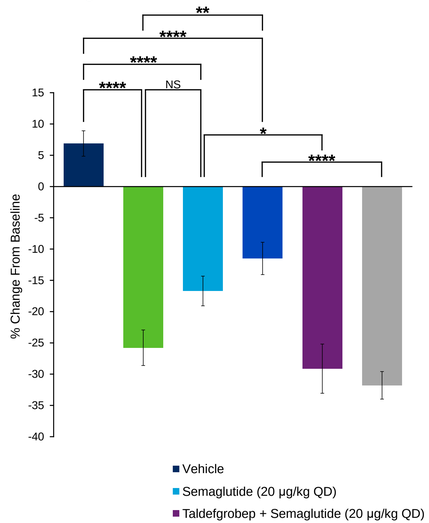
Table 1. Change in Fat Mass and Lean Mass With Taldefgrobep ± Semaglutide in a Mouse Model at Week 4

Treatment (dose)	BL FM (g)	W4 FM (g)	Δ FM (g)	Δ FM (%)	BL LM (g)	W4 LM (g)	Δ LM (g)	Δ LM (%)
Vehicle	18.55	19.74	**1.19**	**6.4**	27.50	29.29	**1.79**	**6.5**
Taldefgrobep (100 mg/kg BIW)	18.85	14.04	**-4.81**	**-25.5**	27.55	31.60	**4.05**	**14.7**
Semaglutide (20 µg/kg QD)	19.36	16.13	**-3.23**	**-16.7**	27.59	28.45	**0.86**	**3.1**
Semaglutide (40 µg/kg QD)	19.03	16.82	**-2.21**	**-11.6**	27.52	27.57	**0.05**	**0.02**
Taldefgrobep + semaglutide (20 µg/kg QD)	18.90	13.43	**-5.47**	**-28.9**	27.32	31.44	**4.12**	**15.1**
Taldefgrobep + semaglutide (40 µg/kg QD)	18.88	12.80	**-6.08**	**-32.2**	27.39	30.92	**3.53**	**12.9**

Δ, change; BIW, twice weekly; BL, baseline; FM, fat mass; LM, lean mass; QD, once daily; W4, Week 4.

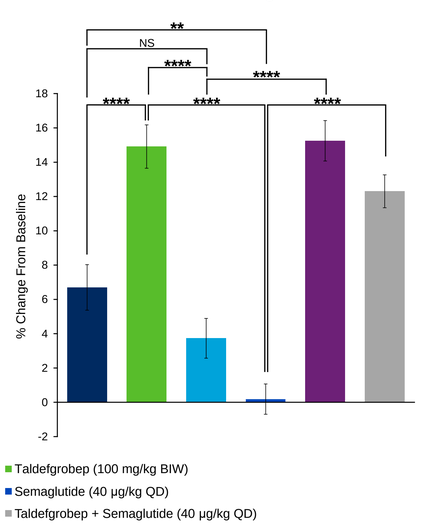
- At 4 weeks, taldefgrobep monotherapy reduced baseline total body weight by 3.5% (-6.7% relative to vehicle)
  - The greatest reduction in baseline total body weight was observed with taldefgrobep + semaglutide 40 µg/kg: -7.6% (-10.8% below vehicle)

Figure 3. Taldefgrobep Monotherapy and Combination Therapy Resulted in Greater Reductions in Fat Mass Than Semaglutide Alone



Error bars represent standard error of the mean. Significance evaluated using Tukey's multiple comparisons test. *P<0.05; **P<0.01; ****P<0.0001.
BIW, twice weekly; NS, not significant; QD, once daily.

Figure 4. Taldefgrobep Monotherapy Increased Lean Muscle Mass and Combination Therapy Prevented Muscle Loss Observed With Semaglutide Alone



Error bars represent standard error of the mean. Significance evaluated using Tukey's multiple comparisons test. **P<0.01; ****P<0.0001.
BIW, twice weekly; NS, not significant; QD, once daily.

CONCLUSIONS

- In an obese mouse model, taldefgrobep demonstrated significant reductions in fat mass and body weight while increasing lean mass
- In combination with a GLP-1 receptor agonist, taldefgrobep yielded an additive effect in fat loss while maintaining its efficacy in promoting significant lean mass gain
- The results from this study support the development of taldefgrobep as a monotherapy and in combination with GLP-1 receptor agonists to reduce fat while maintaining lean mass in individuals living with overweight and obesity

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DISCLOSURES: CB, **CB**, **VG**, **BC**, **CJ**, **PA**, and **VC** are employed by and hold stock/stock options in Biohaven Pharmaceuticals. **A** and **SJL** have nothing to disclose.

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